

## REMARKS

The Office Action consisted of one rejection of the claims under 35 USC §102 and one rejection of the claims under 35 USC §103. Each of these rejections will be responded to below.

### a. Response to §102 Rejections

Claims 1-4, 6-11, 14-19 and 21-23 were rejected under 35 USC §102(b) as being anticipated by Crandall (U.S. 5,560,910).

In order to anticipate a claim, the reference must show each and every element that is contained in a claim (MPEP 2131). By the present amendment, Applicant has amended the claims to include elements that are not shown by the Crandall reference.

Specifically, Applicant has amended independent claims 1 and 10 to recite that the treatment composition set forth therein includes a macrolide antibiotic. Independent claim 18 is further limited to the use of the macrolide antibiotics selected from azithromycin, erythromycin, and roxithromycin.

Crandall does not show the use of macrolide antibiotics. The term "macrolide antibiotics" defines a group of compounds having a characteristic structure, namely a large "macrolidic" ring. As is noted in Applicant's specification, examples of macrolide antibiotics include azithromycin, erythromycin, clarithromycin and roxithromycin.

Crandall does not disclose the use of macrolide antibiotics. Crandall states only in a general sense that the composition might include "antibacterial, antifungal, antiprotozoal, or antiviral agents" (of which there are thousands, or perhaps tens of thousands), and makes no mention of macrolide antibiotics.

As stated above, Applicant's independent claims 1, 10 and 18 and their respective dependents, as amended herein, include elements that expressly require the use of macrolide antibiotics. Crandall does not show this element and therefore fails to anticipate the claims. Applicant therefore respectfully submits that the rejection under 35 USC §102 has been overcome by the present amendment.

### b. Response to §103 Rejections

Claims 1-23 were rejected under 35 USC §103(a) over Crandall in combination with Gupta (U.S. 6,281,199) and “current knowledge in the art.” Applicant respectfully traverses this rejection.

In making the rejection, the Examiner notes that Crandall does not teach the use of azithromycin, erythromycin, or roxithromycin. Gupta is cited as showing use of azithromycin to treat arteriosclerosis, and it is stated that “as it is known in the art that Chlamydia is believed to be responsible for musculoskeletal disease (instant specification Page 6), the use of azithromycin and a penetrating agent for topically treating inflammation would have been known to one of ordinary skill in the art. Motivation to use a penetrating agent with azithromycin would have arisen in order to allow a therapeutically effective amount of azithromycin to reach the Chlamydia infection, which is likely the cause of the inflammation.”

Applicant respectfully disagrees. In order to establish a *prima facie* case of obviousness, there must be some suggestion or motivation in the prior art to modify the reference or combine the references, and there must be a reasonable expectation of success: the teaching or suggestion to make a claimed combination and the reasonable expectation of success must both be found in the prior art, not in the Applicant’s disclosure. (MPEP 2143) However, the assertion that “Chlamydia is believed to be responsible for musculoskeletal disease” and that motivation “would have arisen in order to allow a therapeutically effective amount of azithromycin to reach the Chlamydia infection, which is likely the cause of the inflammation” is not found in the prior art, but is instead based on Applicant’s own disclosure. Applicant’s disclosure makes it clear that this belief is Applicant’s own hypothesis, not an admission of prior art. Therefore, this information cannot be relied on to establish obviousness.

Furthermore, the cited art itself does not provide any motivation for the proposed combination. Gupta teaches the oral administration of azithromycin in an effort to eradicate Chlamydia infections within the circulatory system, i.e., the bloodstream. The reference shows no recognition of using azithromycin to alleviate inflammation within the musculoskeletal system and other soft tissues. Consequently, neither this reference nor Crandall provides any motivation for employing azithromycin (or other macrolide antibiotics) and a penetrating agent so as to reach into such tissues.

The Office Action therefore fails to establish the first leg required for a *prima facie* case of obviousness, i.e., no suggestion or motivation has been shown for making the proposed combination. The Office Action also fails to establish the second step in a *prima facie* case of obviousness, i.e., a reasonable expectation of success.

The Office Action assumes that because Crandall teaches that a proteolytic enzyme may be used with a penetrating agent and possibly some "antibacterial, antifungal, antiprotozoal, or antiviral agents", then use of azithromycin or other macrolide antibiotic in this combination would be successful. However, the references provide no support for this assumption. The proteolytic enzymes of Crandall bear no structural resemblance whatsoever to macrolide antibiotics. As can be seen in the attached illustration of capsaicin, proteolytic enzymes are comparatively simple compounds with mostly chain-like structures. By comparison, as can be seen in the attached illustrations of azithromycin, clarithromycin and erythromycin, macrolide antibiotics are complex compounds that include large macrocyclic rings and first and second ancillary ring structures. Given these structural dissimilarities, one of ordinary skill in the art would not have had a reasonable expectation of success for the use of azithromycin in the composition that is taught by Crandall. As for Crandall's reference to "antibacterial, antifungal, antiprotozoal, or antiviral agents", represents a range of substances so broad and disparate in character as to provide no teaching regarding an expectation of success for the use of macrolide antibiotics.

Accordingly, for the reasons discussed above, the cited art fails to provide any suggestion or motivation for using azithromycin or another macrolide antibiotic in the compositions of Crandall, and also fails to provide any reasonable expectation of success for such use. The Office Action therefore fails to establish a *prima facie* case of obviousness against those claims that require the use of a macrolide antibiotic. Since Applicant's amended claims all include a limitation requiring the use of a macrolide antibiotic, Applicant respectfully requests that the rejection of the claims under 35 USC §103 be reconsidered and withdrawn.

c. Other amendments

The dependency of claims 5 and 12 has been amended in view of the cancellation of claims 4 and 11 by the present amendment.

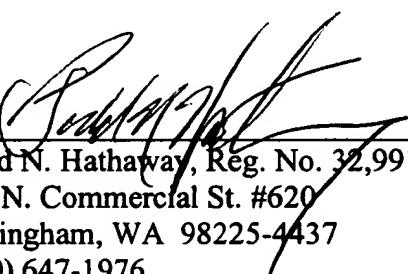
d. Conclusion

Applicant respectfully requests reconsideration of the present application in view of the amendments and remarks set forth herein. It is believed that the above-referenced claims are now in condition for allowance. If there is any matter that can be expedited by consultation with Applicant's attorney, such would be welcome. Applicant's attorney can normally be reached at the telephone number given below.

Signed at Bellingham, County of Whatcom, State of Washington this 26<sup>th</sup> day of April 2002.

Respectfully submitted,

DAVID M. ALLEN

By   
Todd N. Hathaway, Reg. No. 32,991  
119 N. Commercial St. #620  
Bellingham, WA 98225-4437  
(360) 647-1976

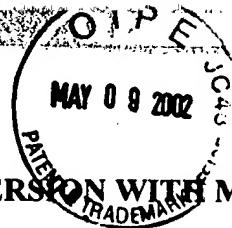
CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that this paper (along with any paper referred to in the attached sheet or enclosed) is being deposited with the United States Postal Service as first class mail in an envelope addressed to Commissioner of Patents and Trademarks, Washington, D.C. 20231, on the date shown below.

4-26-02  
Date

Dale Y Perez  
(Print name of person mailing paper)

Dale Y Perez  
(Signature of person mailing paper)



## VERSION WITH MARKINGS TO SHOW CHANGES MADE (CLAIMS)

1. (amended) A method for alleviating a disease state resulting from a microbial infection affecting sub-dermal soft tissue in a predetermined area of the body, said method comprising the steps of:

providing a treatment composition comprising, in combination:

- (iii) a selected [antimicrobial compound] macrolide antibiotic; and
- (iv) a selected mobilizing agent in an amount sufficient to enable said antimicrobial compound to penetrate into said sub-dermal soft tissue; and

applying said treatment composition to said predetermined area of the body so that said antimicrobial compound penetrates said sub-dermal soft tissue so as to reach said microbial infection therein.

5. (amended) The method of claim [4] 1, wherein the step of providing said treatment composition comprises:

selecting said antimicrobial compound from the group consisting of azithromycin, erythromycin and roxithromycin.

10. (amended) A treatment composition for alleviating a disease state resulting from a microbial infection affecting sub-dermal soft tissue in a predetermined area of the body, said treatment composition comprising:

- (iii) a selected [antimicrobial compound] macrolide antibiotic; and
- (iv) a selected mobilizing agent in an amount sufficient to enable said antimicrobial compound to penetrate into said sub-dermal soft tissue so as to reach said microbial infection therein when said composition is applied to said predetermined area of the body.

12. (amended) The treatment composition of claim [11] 10, wherein said macrolide antibiotic composition is selected from the group consisting of azithromycin, erythromycin and roxithromycin

This Page Is Inserted by IFW Operations  
and is not a part of the Official Record

## **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

**IMAGES ARE BEST AVAILABLE COPY.**

As rescanning documents *will not* correct images,  
please do not report the images to the  
Image Problem Mailbox.

Intestinal amebiasis: Adults: 500 mg every 12 hours, 333 mg every 8 hours or 250 mg every 6 hours for 10 to 14 days. Children: 30 to 50 mg/kg/day in divided doses for 10 to 14 days.

Pertussis: Although optimal dosage and duration have not been established, doses of erythromycin utilized in reported clinical studies were 40 to 50 mg/kg/day, given in divided doses for 5 to 14 days.

Legionnaires' Disease: Although optimal dosage has not been established, doses utilized in reported clinical data were 1 to 4 g daily in divided doses.

#### HOW SUPPLIED

**ERYTHROCIN STEARATE** Filmtab Tablets (erythromycin stearate tablets, USP) are supplied in the following strengths and packages:

<b>ERYTHROCIN STEARATE</b> Filmtab, 250 mg pink tablets imprinted with the corporate logo  and the Abbo-Code designation ES- Bottles of 100 .....	(NDC 0074-6346-20)
Bottles of 500 .....	(NDC 0074-6346-53)
Bottles of 1000 .....	(NDC 0074-6346-19)

ABBO-PAQ® unit dose strip packages of 100 tablets .....

..... (NDC 0074-6346-38)

**ERYTHROCIN STEARATE** Filmtab, 500 mg pink tablets imprinted with the corporate logo  and the Abbo-Code designation ET-  
Bottles of 100 .....

..... (NDC 0074-6316-13)

Recommended Storage: Store below 86°F (30°C).

#### REFERENCES

1. National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*, Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25 NCCLS, Villanova, PA, December 1993.

2. National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Disk Susceptibility Tests*, Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24 NCCLS, Villanova, PA, December 1993.

3. Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, the American Heart Association: Prevention of Rheumatic Fever. *Circulation*, 78(4):1082-1086, October 1988. (nursing home patients) (see also reference 19)

4. Data on file, Abbott Laboratories, North Chicago, IL. Ref. 03-5083-R14

5. Revised; November, 2000

ABBOTT LABORATORIES  
NORTH CHICAGO, IL 60064, U.S.A.

PRINTED IN U.S.A.  
Shown in Product Identification Guide, page 903

© 2000 Abbott Laboratories. All rights reserved.

Erythromycin Base Filmtab®  
ERYTHROMYCIN TABLETS, USP

B only

Product of U.S.A. Manufactured by Abbott Laboratories

DESCRIPTION

Erythromycin Base Filmtab (erythromycin tablets, USP) is an antibiotic product containing erythromycin, USP, in a unique, nonenteric film coating for oral administration.

Erythromycin Base Filmtab tablets are available in two strengths containing either 250 mg or 500 mg of erythromycin base.

Erythromycin is produced by a strain of *Saccharopolyspora erythraea* (formerly *Streptomyces erythraeus*) and belongs to the macrolide group of antibiotics. It is basic and readily forms salts with acids. Erythromycin is a white to off-white powder, slightly soluble in water, and soluble in alcohol, chloroform, and ether. Erythromycin is known chemically as (3R\*, 4S\*, 5S\*, 6R\*, 7R\*, 9R\*, 11R\*, 12R\*, 13S\*, 14R\*)-4-((2,6-dideoxy-3-C-methyl-3-O-methyl-a-L-ribo-hexopyranosyl)oxy)-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xyo-hexopyranosyl]oxy]oxacyclotetradeac-2,10-dione. The molecular formula is C<sub>37</sub>H<sub>67</sub>NO<sub>13</sub>, and the molecular weight is 733.94. The structural formula is:



A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can

achieve concentrations in the infected tissue that may be inhibitory to the pathogen. Variations in the absorption of erythromycin are, however, observed and some patients do not achieve optimal serum levels. Erythromycin is largely bound to plasma proteins. After absorption, erythromycin diffuses readily into most body fluids. In the absence of meningeal inflammation, low concentrations are normally achieved in the spinal fluid but the passage of the drug across the blood-brain barrier increases in meningitis. Erythromycin crosses the placental barrier, but fetal plasma levels are low. The drug is excreted in human milk. Erythromycin is not removed by peritoneal dialysis or hemodialysis.

In the presence of normal hepatic function, erythromycin is concentrated in the liver and is excreted in the bile; the effect of hepatic dysfunction on biliary excretion of erythromycin is not known. After oral administration, less than 5% of the administered dose can be recovered in the active form in the urine. Optimal blood levels are obtained when Erythromycin Base Filmtab tablets are given in the fasting state (at least 1/2 hour and preferably 2 hours before meals). Bioavailability data are available from Abbott Laboratories, Dept. 42W.

**Microbiology:**

Erythromycin acts by inhibition of protein synthesis by binding 50 S ribosomal subunits of susceptible organisms. It does not affect nucleic acid synthesis. Antigenicity has been demonstrated *in vitro* between erythromycin and clindamycin, lincomycin, and chloramphenicol.

Many strains of *Haemophilus influenzae* are resistant to erythromycin alone, but are susceptible to erythromycin and sulfonamides used concomitantly.

Staphylococci resistant to erythromycin may emerge during a course of erythromycin therapy. Erythromycin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section.

Gram-positive organisms:

*Corynebacterium diphtheriae*

*Corynebacterium minutissimum*

*Listeria monocytogenes*

*Staphylococcus aureus* (resistant organisms may emerge during treatment)

*Streptococcus pneumoniae*

*Streptococcus pyogenes*

Gram-negative organisms:

*Bordetella pertussis*

*Legionella pneumophila*

*Neisseria gonorrhoeae*

Other microorganisms:

*Chlamydia trachomatis*

*Entamoeba histolytica*

*Mycoplasma pneumoniae*

*Treponema pallidum*

*Ureaplasma urealyticum*

The following *in vitro* data are available, but their clinical significance is unknown.

Erythromycin exhibits *in vitro* minimal inhibitory concentrations (MICs) of 0.5 µg/mL or less against most ( $\geq 90\%$ ) strains of the following microorganisms; however, the safety and effectiveness of erythromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Gram-positive organisms:

Viridans group streptococci

Gram-negative organisms:

*Moraxella catarrhalis*

**Susceptibility Tests:**

**Dilution Techniques:**

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of erythromycin powder. The MICs should be interpreted according to the following criteria:

MIC (µg/mL)	Interpretation
$\leq 0.5$	Susceptible (S)
1-4	Intermediate (I)
$\geq 8$	Resistant (R)

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can

achieve concentrations in the infected tissue that may be inhibitory to the pathogen.

**Microorganism**

*S. aureus* ATCC 29213 0.12-0.5

*E. faecalis* ATCC 29212 1

**Diffusion Techniques: Media, Inoculum, Results:**

Quantitative methods that require measurement of some parameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 15 µg erythromycin to test the susceptibility of microorganisms to erythromycin. Reports from the laboratory providing results of the standard single-disk susceptibility test with a 15 µg erythromycin disk should be interpreted according to the following criteria:

**Zone Diameter (mm) Interpretation**

$\geq 23$  Susceptible (S)

14-22 Intermediate (I)

$\leq 13$  Resistant (R)

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC of erythromycin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms to assure control of technical aspects of the laboratory procedures. For the diffusion technique, the 15 µg erythromycin disk should provide the following zone diameters in these laboratory test quality control strains:

**Microorganism Zone Diameter (mm)**

*S. aureus* ATCC 25923 19.0-21.0 22-30

*E. faecalis* ATCC 25924 15.0-17.0 15-20

#### INDICATIONS AND USAGE

Erythromycin Base Filmtab tablets are indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below.

Upper respiratory tract infections of mild to moderate degree caused by *Streptococcus pyogenes*; *Streptococcus pneumoniae*; *Haemophilus influenzae* (when used concomitantly with adequate doses of sulfonamides, since many strains of *H. influenzae* are not susceptible to the erythromycin concentrations ordinarily achieved) (See appropriate sulfonamide labeling for prescribing information.)

Lower respiratory tract infections of mild to moderate severity caused by *Streptococcus pyogenes* or *Streptococcus pneumoniae*.

Listeriosis caused by *Listeria monocytogenes*.

Respiratory tract infections due to *Mycoplasma pneumoniae*.

Skin and skin structure infections of mild to moderate severity caused by *Streptococcus pyogenes* or *Staphylococcus aureus* (resistant staphylococci may emerge during treatment).

Pertussis (whooping cough) caused by *Bordetella pertussis*.

Erythromycin is effective in eliminating the organism from the nasopharynx of infected individuals, rendering them noninfectious. Some clinical studies suggest that erythromycin may be helpful in the prophylaxis of pertussis in exposed susceptible individuals.

Diphtheria: Infections due to *Corynebacterium diphtheriae* as an adjunct to antitoxin, to prevent establishment of carriers and to eradicate the organism in carriers.

Erythrasma—in the treatment of infections due to *Corynebacterium minutissimum*.

Intestinal amebiasis caused by *Entamoeba histolytica* (oral erythromycin only). Extraenteric amebiasis requires treatment with other agents.

Acute pelvic inflammatory disease caused by *Neisseria gonorrhoeae*: Erythrocin® Lactobionate I.V. (erythromycin lactobionate for injection, USP) followed by erythromycin base orally, as an alternative drug in treatment of acute pelvic inflammatory disease caused by *N. gonorrhoeae* in female patients with a history of sensitivity to penicillin. Patients should have a serologic test for syphilis before receiving erythromycin as treatment of gonorrhea and a follow-up serologic test for syphilis after 3 months.

Erythromycins are indicated for treatment of the following infections caused by *Chlamydia trachomatis*: conjunctivitis of the newborn, pneumonia of infancy, and urogenital infections during pregnancy. When tetracyclines are contraindicated or not tolerated, erythromycin is indicated for the treatment of uncomplicated urethral, endocervical, or rectal infections in adults due to *Chlamydia trachomatis*.

©2000 Knoll Pharmaceutical Company.  
AKINETON is a registered trademark of Knoll AG.

Manufactured for:

PARK PHARMACEUTICAL INC.

Spring Valley, New York 10577

Manufactured by:

Knoll Laboratories

A Division of

Knoll Pharmaceutical Company

Mount Olive, New Jersey 07828

Issued: 08/00

09000023

Shown in Product Identification Guide, page 303.

### BIAXIN Filmtab®

(clarithromycin tablets, USP)

### BIAXIN® XL Filmtab®

(clarithromycin extended-release tablets)

### BIAXIN® Granules

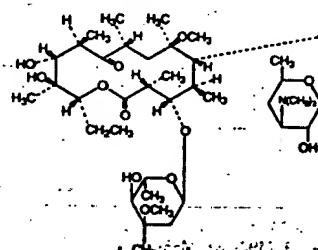
(clarithromycin for oral suspension, USP)

Rx only

B

### DESCRIPTION

Clarithromycin is a semi-synthetic macrolide antibiotic. Chemically, it is 6-O-methylerythromycin. The molecular formula is  $C_{29}H_{49}NO_{13}$ , and the molecular weight is 747.96. The structural formula is:



Clarithromycin is a white to off-white crystalline powder. It is soluble in acetone, slightly soluble in methanol, ethanol, and acetonitrile, and practically insoluble in water. BIAXIN is available as immediate-release tablets, extended-release tablets, and granules for oral suspension. Each yellow oval film-coated immediate-release BIAXIN tablet contains 250 mg or 500 mg of clarithromycin and the following inactive ingredients:

250 mg tablets: hydroxypropyl methylcellulose, hydroxypropyl cellulose, colloidal silicon dioxide, croscarmellose sodium, D&C Yellow No. 10, FD&C Blue No. 1, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch, propylene glycol, silicon dioxide, sorbic acid, sorbitan monolaurate, stearic acid, talc, titanium dioxide, and vanillin.

500 mg tablets: hydroxypropyl methylcellulose, hydroxypropyl cellulose, colloidal silicon dioxide, croscarmellose sodium, D&C Yellow No. 10, magnesium stearate, microcrystalline cellulose, povidone, propylene glycol, sorbic acid, sorbitan monolaurate, talc, titanium dioxide, and vanillin.

Each yellow oval film-coated BIAXIN XL tablet contains 500 mg of clarithromycin and the following inactive ingredients: cellulose polymers, D&C Yellow No. 10, lactose monohydrate, magnesium stearate, propylene glycol, sorbic acid, sorbitan monolaurate, talc, titanium dioxide, and vanillin.

After constitution, each 5 mL of BIAXIN suspension contains 125 mg or 250 mg of clarithromycin. Each bottle of BIAXIN granules contains 1250 mg (50 mL size), 2500 mg (50 and 100 mL sizes), or 5000 mg (100 mL size) of clarithromycin and the following inactive ingredients: carobomer, castor oil, citric acid, hypromellose phthalate, maltodextrin, potassium sorbate, povidone, silicon dioxide, sucrose, xanthan gum, titanium dioxide and fruit punch flavor.

### CLINICAL PHARMACOLOGY

#### Pharmacokinetics:

Clarithromycin is rapidly absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability of 250-mg clarithromycin tablets was approximately 50%. For a single 500-mg dose of clarithromycin, food slightly delays the onset of clarithromycin absorption; increasing the peak time from approximately 2 to 2.5 hours. Food also increases the clarithromycin peak plasma concentration by about 24%, but does not affect the extent of clarithromycin bioavailability. Food does not affect the onset of formation of the antimicrobially active metabolite, 14-OH clarithromycin or its peak plasma concentration but does slightly decrease the extent of metabolite formation, indicated by an 11% decrease in area under the plasma concentration-time curve (AUC). Therefore, BIAXIN tablets may be given without regard to food.

In nonfasting healthy human subjects (males and females), peak plasma concentrations were attained within 2 to 3 hours after oral dosing. Steady-state peak plasma clarithromycin concentrations were attained within 3 days and were approximately 1 to 2  $\mu$ g/mL with a 250-mg dose administered every 12 hours and 3 to 4  $\mu$ g/mL with a 500-mg dose

every 12 hours administered every 8 to 12 hours. The bioavailability of clarithromycin pharmacokinetics is slight at the recommended doses of 250 mg and 500 mg administered every 8 to 12 hours. With a 250 mg every 12 hours dosing, the principal metabolite, 14-OH clarithromycin, attains a peak steady-state concentration of about 0.6  $\mu$ g/mL and has an elimination half-life of 5 to 6 hours. With a 500 mg every 8 to 12 hours dosing, the peak steady-state concentration of 14-OH clarithromycin is slightly higher (up to 1  $\mu$ g/mL), and its elimination half-life is about 7 to 9 hours. With any of these dosing regimens, the steady-state concentration of this metabolite is generally attained within 3 to 4 days. After a 250-mg tablet every 12 hours, approximately 20% of the dose is excreted in the urine as clarithromycin, while after a 500-mg tablet every 12 hours, the urinary excretion of clarithromycin is somewhat greater, approximately 30%. In comparison, after an oral dose of 250 mg (125 mg/5 mL) suspension every 12 hours, approximately 40% is excreted in urine as clarithromycin. The renal clearance of clarithromycin is, however, relatively independent of the dose size and approximates the normal glomerular filtration rate. The major metabolite found in urine is 14-OH clarithromycin, which accounts for an additional 10% to 15% of the dose with either a 250-mg or a 500-mg tablet administered every 12 hours.

Steady-state concentrations of clarithromycin and 14-OH clarithromycin observed following administration of 500-mg doses of clarithromycin every 12 hours to adult patients with HIV infection were similar to those observed in healthy volunteers. In adult HIV-infected patients taking 500- or 1000-mg doses of clarithromycin every 12 hours, steady-state clarithromycin  $C_{max}$  values ranged from 2 to 4  $\mu$ g/mL and 5 to 10  $\mu$ g/mL, respectively. The steady-state concentrations of clarithromycin in subjects with impaired hepatic function did not differ from those in normal subjects; however, the 14-OH clarithromycin concentrations were lower in the hepatically impaired subjects. The decreased formation of 14-OH clarithromycin was at least partially offset by an increase in renal clearance of clarithromycin in the subjects with impaired hepatic function compared to healthy subjects.

The pharmacokinetics of clarithromycin was also altered in subjects with impaired renal function. (See PRECAUTIONS and DOSAGE AND ADMINISTRATION.)

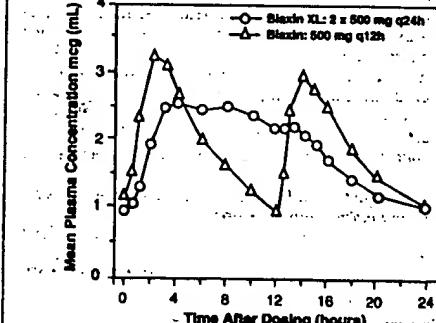
Clarithromycin and the 14-OH clarithromycin metabolite distribute readily into body tissues and fluids. There are no data available on cerebrospinal fluid penetration. Because of high intracellular concentrations, tissue concentrations are higher than serum concentrations. Examples of tissue and serum concentrations are presented below.

CONCENTRATION (mg/L) (after 250 mg q12h)

Tissue Type	Tissue (μg/g)	Serum (ng/mL)
Tonsil	1.6	0.8
Lung	8.8	1.7

Clarithromycin extended-release tablets provide extended absorption of clarithromycin from the gastrointestinal tract after oral administration. Relative to an equal total daily dose of immediate-release clarithromycin tablets, clarithromycin extended-release tablets provide lower and later steady-state peak plasma concentrations but equivalent 24-hour AUC's for both clarithromycin and its microbiologically-active metabolite, 14-OH clarithromycin. While the extent of formation of 14-OH clarithromycin following administration of BIAXIN XL tablets (2 × 500 mg once daily) is not affected by food, administration under fasting conditions is associated with approximately 30% lower clarithromycin AUC relative to administration with food. Therefore, BIAXIN XL tablets should be taken with food.

Steady-State Clarithromycin Plasma Concentration-Time Profiles



In healthy human subjects, steady-state peak plasma clarithromycin concentrations of approximately 2 to 3  $\mu$ g/mL were achieved about 5 to 8 hours after oral administration of 2 × 500 mg BIAXIN XL tablets once daily; for

Continued on next page

(top of previous page) 5%.

In this study, the incidence of adverse events was gastrointestinal; in all patients treated a common side effect was diarrhea (4%).

Several comparative clinical and microbiologic studies performed in the United States, compared to an antimicrobial/beta-lactam study utilized two of the same investigators (Protocol 2 (above), and these two investigators in Efficacy Protocol 3). Efficacy Protocol 3 was not considered to be a study. Significant rates of beta-lactamase (20%) were found. Ninety-two (92) patients were available for clinical and microbiologic efficacy. Clinical success rate (i.e., cure and improvement with a baseline pathogen at the Day 14 visit) for azithromycin vs. 100% for control; at Day 30 the clinical success rate was 82% for 80% for control.

Examinations were made at the pre-treatment visit and were reassessed at later visits. At Day 30 visits, the following presumptive cure outcomes (i.e., clinical success) were available in the evaluable group:

(on previous page)

Analysis of the above study, the incidence of primarily gastrointestinal, in all patients with azithromycin and 31% with the control. Common side effect was diarrhea/loose stool (vs. 29% control).

Additional controlled studies, conducted in the United States, showed azithromycin (12 mg/kg once a day for 5 days) to penicillin V (250 mg three times a day) in the treatment of pharyngitis due to *Group A* hemolytic streptococci (GABHS) or *S. pyogenes*. Azithromycin was clinically and microbiologically equivalent to penicillin at Day 14 and Day 30. Clinical success (i.e., cure and improvement) efficacy rates (for the combined with documented GABHS):

(on previous page)

Azithromycin-susceptible & *pyogenes* were isolated from following therapy. These events, primarily gastrointestinal (19% on azithromycin and 13% on penicillin), were diarrhea/loose stool (vs. 29% penicillin), vomiting (vs. 4% penicillin), and abdominal pain (vs. 1% penicillin).

**TOXICOLOGY:**

Phagocytosis of cellular phospholipid accumulation has been observed in some tissues of mice, rats, and dogs following azithromycin. It has been demonstrated in various systems (e.g., eye, dorsal root filaments, kidney, spleen, and pancreas) in azithromycin at doses which, expressed only 2 times greater than the recommended dose and in rats at doses comparable to adult human dose. This effect has been observed in all forms of azithromycin treatment. Phagocytosis is observed to a similar extent in the tissue of dogs given daily doses of azithromycin for 10 days to 30 days. Based on pharmacokinetic studies has been seen in the rat (30 mg/kg/day) and in man (30 mg/m<sup>2</sup>/day). The observed  $C_{max}$  value of 1.3  $\mu\text{g}/\text{mL}$  (6 times the mean  $C_{max}$ ) and drug dose in the population). On mg/m<sup>2</sup> basis, 30 mg/kg (79 mg/m<sup>2</sup>) and 10 mg/kg dose in the dog (79 mg/m<sup>2</sup>) are 0.4 and 0.6 times, respectively, the mean  $C_{max}$  of the pediatric patients with an average of 1.5  $\mu\text{g}/\text{mL}$  (79 mg/m<sup>2</sup>). This effect, similar to that seen in humans, is reversible after cessation of azithromycin. The significance of these findings for animals is unknown.

Guidelines for Clinical Laboratory Standards. Document Antimicrobial Susceptibility Tests—4th Edition—Aerobic—Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 12, NCCLS, Villanova, PA, December 1993.

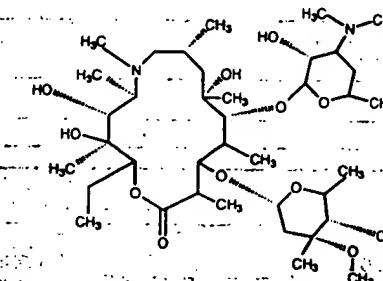
Guidelines for Clinical Laboratory Standards. Document Antimicrobial Disk Susceptibility Test—4th Edition: Approved Standard NCCLS Document M2-A3, Vol. 13, No. 24, NCCLS, Villanova, PA, December 1993.

© 2001 PFIZER INC.

Revised January 2001  
Product Identification Guide, page 331.

## DESCRIPTION

ZITHROMAX® (azithromycin capsules, azithromycin tablets and azithromycin for oral suspension) contain the active ingredient azithromycin, an azalide, a subclass of macrolide antibiotics, for oral administration. Azithromycin has the chemical name (2R, 3S, 4R, 5R, 8R, 10R, 11R, 12S, 13S, 14R)-13-[(2,6-dideoxy-3-C-methyl-3-O-methyl-a-L-ribo-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[3(4,6-trideoxy-3-(dimethylamino)-6-D-xylo-hexopyranosyl)oxy]-1-oxa-6-azacyclotetradecan-15-one. Azithromycin is derived from erythromycin; however, it differs chemically from erythromycin in that a methyl-substituted nitrogen atom is incorporated into the lactone ring. Its molecular formula is  $C_{38}H_{72}N_2O_{12}$ , and its molecular weight is 749.0. Azithromycin has the following structural formula:



Azithromycin, as the dihydrate, is a white crystalline powder with a molecular formula of  $C_{38}H_{72}N_2O_{12} \cdot 2H_2O$  and a molecular weight of 785.0.

ZITHROMAX® capsules contain azithromycin dihydrate equivalent to 250 mg of azithromycin. The capsules are supplied in red opaque hard-gelatin capsules (containing FD&C Red #40). They also contain the following inactive ingredients: anhydrous lactose, corn starch, magnesium stearate, and sodium lauryl sulfate.

ZITHROMAX® tablets contain azithromycin dihydrate equivalent to 600 mg azithromycin. The tablets are supplied as white, modified oval-shaped, film-coated tablets. They also contain the following inactive ingredients: dibasic calcium phosphate anhydrous, pregelatinized starch, sodium croscarmellose, magnesium stearate, sodium lauryl sulfate and an aqueous film coat consisting of hydroxypropyl methyl cellulose, titanium dioxide, lactose and triacetin.

ZITHROMAX® for oral suspension is supplied in a single dose packet containing azithromycin dihydrate equivalent to 1 g azithromycin. It also contains the following inactive ingredients: colloidal silicon dioxide, sodium phosphate tribasic anhydrous, spray dried artificial banana flavor, spray dried artificial cherry flavor, and sucrose.

## CLINICAL PHARMACOLOGY

**Pharmacokinetics:** Following oral administration, azithromycin is rapidly absorbed and widely distributed throughout the body. Rapid distribution of azithromycin into tissues and high concentrations within cells result in significantly higher azithromycin concentrations in tissues than in plasma or serum. The 1 g single dose packet is bioequivalent to 250 mg capsules. The pharmacokinetic parameters of azithromycin in plasma after dosing as per labeled recommendations in healthy young adults and asymptomatic HIV-seropositive adults (age 18–40 years old) are portrayed in the following chart [See first table at top of next page].

In these studies (500 mg Day 1; 250 mg Days 2–5), there was no significant difference in the disposition of azithromycin between male and female subjects. Plasma concentrations of azithromycin following single 500 mg oral and i.v. doses declined in a polyphasic pattern resulting in an average terminal half-life of 68 hours. With a regimen of 500 mg on Day 1 and 250 mg/day on Days 2–5,  $C_{min}$  and  $C_{max}$  remained essentially unchanged from Day 2 through Day 5 of therapy. However, without a loading dose, azithromycin  $C_{max}$  levels required 5 to 7 days to reach steady-state.

In asymptomatic HIV-seropositive adult subjects receiving 600-mg ZITHROMAX® tablets once daily for 22 days, steady state azithromycin serum levels were achieved by Day 15 of dosing.

When azithromycin capsules were administered with food, the rate of absorption ( $C_{max}$ ) of azithromycin was reduced by 52% and the extent of absorption (AUC) by 43%.

When the oral suspension of azithromycin was administered with food, the  $C_{max}$  increased by 46% and the AUC by 14%.

The absolute bioavailability of two 600 mg tablets was 34% ( $CV=56\%$ ). Administration of two 600 mg tablets with food increased  $C_{max}$  by 31% ( $CV=43\%$ ) while the extent of absorption (AUC) was unchanged (mean ratio of AUCs = 1.00;  $CV=55\%$ ).

The AUC of azithromycin in 250 mg capsules was unaffected by coadministration of an antacid containing aluminum and magnesium hydroxide with ZITHROMAX® (azithromycin); however, the  $C_{max}$  was reduced by 24%. Administration of cimetidine (800 mg) two hours prior to azithromycin had no effect on azithromycin absorption.

Although higher peak concentrations (increased by 20 to 50%) were observed, no significant accumulation occurred. The high values in adults (or apparent steady-state volume of distribution (31.1 l)) and plasma clearance (600 ml/min) suggest that the prolonged half-life is due to extensive uptake and subsequent release of drug from tissue. Selected tissue (or fluid) concentration and tissue (or fluid) to plasma/serum concentration ratios are shown in the following table:

[See second table on next page]

The extensive tissue distribution was confirmed by examination of additional tissues and fluids (bone, ejaculate, prostate, ovary, uterus, salpinx, stomach, liver, and gallbladder). As there are no data from adequate and well-controlled studies of azithromycin treatment of infections in these additional body sites, the clinical significance of these tissue concentration data is unknown.

Following a regimen of 500 mg on the first day and 250 mg daily for 4 days, only very low concentrations were noted in cerebrospinal fluid (less than 0.01  $\mu\text{g}/\text{mL}$ ) in the presence of non-inflamed meninges.

Following oral administration of a single 1200 mg dose (two 600 mg tablets), the mean maximum concentration in peripheral leukocytes was 140  $\mu\text{g}/\text{mL}$ . Concentrations remained above 32  $\mu\text{g}/\text{mL}$  for approximately 60 hr. The mean half-lives for 6 males and 6 females were 34 hr and 57 hr, respectively. Leukocyte to plasma  $C_{max}$  ratios for males and females were 258 ( $\pm 77\%$ ) and 175 ( $\pm 60\%$ ), respectively, and the AUC ratios were 804 ( $\pm 31\%$ ) and 541 ( $\pm 28\%$ ), respectively. The clinical relevance of these findings is unknown.

Following oral administration of multiple daily doses of 600 mg (1 tablet/day) to asymptomatic HIV-seropositive adults, mean maximum concentration in peripheral leukocytes was 252  $\mu\text{g}/\text{mL}$  ( $\pm 49\%$ ). Trough concentrations in peripheral leukocytes at steady-state averaged 146  $\mu\text{g}/\text{mL}$  ( $\pm 33\%$ ). The mean leukocyte to serum  $C_{max}$  ratio was 456 ( $\pm 38\%$ ) and the mean leukocyte to serum AUC ratio was 816 ( $\pm 31\%$ ). The clinical relevance of these findings is unknown.

The serum protein binding of azithromycin is variable in the concentration range approximating human exposure, decreasing from 51% at 0.02  $\mu\text{g}/\text{mL}$  to 7% at 2  $\mu\text{g}/\text{mL}$ . Biliary excretion of azithromycin, predominantly as unchanged drug, is a major route of elimination. Over the course of a week, approximately 6% of the administered dose appears as unchanged drug in urine.

There are no pharmacokinetic data available from studies in hepatically or renally impaired individuals.

The effect of azithromycin on the plasma levels or pharmacokinetics of theophylline administered in multiple doses adequate to reach therapeutic steady-state plasma levels is not known. [See PRECAUTIONS.]

**Mechanism of Action:** Azithromycin acts by binding to the 50S ribosomal subunit of susceptible microorganisms and, thus, interfering with microbial protein synthesis. Nucleic acid synthesis is not affected.

Azithromycin concentrates in phagocytes and fibroblasts as demonstrated by *in vitro* incubation techniques. Using such methodology, the ratio of intracellular to extracellular concentration was >30 after one hour incubation. *In vivo* studies suggest that concentration in phagocytes may contribute to drug distribution to inflamed tissues.

## Microbiology:

Azithromycin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section.

### Aerobic Gram-Positive Microorganisms

*Staphylococcus aureus*

*Streptococcus agalactiae*

*Streptococcus pneumoniae*

*Streptococcus pyogenes*

**NOTE:** Azithromycin demonstrates cross-resistance with erythromycin-resistant gram-positive strains. Most strains of *Enterococcus faecalis* and methicillin-resistant *staphylococci* are resistant to azithromycin.

### Aerobic Gram-Negative Microorganisms

*Haemophilus influenzae*

*Moraxella catarrhalis*

**Other** Microorganisms

*Chlamydia trachomatis*

Beta-lactamase production should have no effect on azithromycin activity.

Azithromycin has been shown to be active *in vitro* and in the prevention and treatment of disease caused by the following microorganisms:

### Mycobacteria

*Mycobacterium avium* complex (MAC) consisting of:

*Mycobacterium avium*

*Mycobacterium intracellulare*

The following *in vitro* data are available, but their clinical significance is unknown.

Azithromycin exhibits *in vitro* minimal inhibitory concentrations (MICs) of 2.0  $\mu\text{g}/\text{mL}$  or less against most ( $\geq 90\%$ ) strains of the following microorganisms; however, the safety and effectiveness of azithromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

### Aerobic Gram-Positive Microorganisms

*Streptococci* (Groups C, F, G)

*Viridans group streptococci*

*Continued on next page.*

5.4 mg/kg. L. Orö, A. Wretlind, *Acta Pharmacol. Toxicol.* 10, 141 (1961).

use: Manuf of esters for artificial fruit flavors and perfumes; as an intermediate in other chemical syntheses.

**1734. n-Caproic Acid. Hexanoic acid.**  $C_6H_{12}O_2$ ; mol wt 161.6. C 62.04%, H 10.41%, O 27.55%.  $CH_3(CH_2)_4COOH$ . Occurs in milk fats (about 2%), in coconut oil (<1%), various palm and other oils. Prepn: Vliet *et al.*, *Org. Syn. coll. II*, 417 (1943); Reid, Ruhoff, *ibid.*, 475. Manuf by catalytic reduction of corresponding  $\beta$ -lactone: Caldwell, U.S. pat. 2,484,486 (1949 to Kodak); from oleic acid: Follett, Murray, U.S. pat. 2,580,417 (1952 to Arthur D. Little); from castor oil or a ricinoleate: Steadman, Peterson, U.S. pat. 2,847,432 (1958 to National Res. Corp.); by ozonolysis of tall oil unsaturated fatty acids: Maggiolo, U.S. pat. 3,065,937 (1958 to Welsbach); from 1,3-butadiene and potassium acetate in presence of  $NaNH_2$ : Schmerling, Tockelt, U.S. pat. 3,075,010 (1963 to Universal Oil Prod.); from cyclohexanol: Bartlett, Lippincott, U.S. pat. 3,121,728 (1964 to ESSO); by catalytic oxidation of n-hexanol: Hay, U.S. pat. 3,173,933 (1965 to General Electric). Review: *Fatty Acids Part I*, K. S. Markley, Ed. (Interscience, New York, 2nd ed., 1960) pp 34, 37.

Oily liquid, bp 205°. Characteristic goat-like odor. mp 34°.  $d_4^{20}$  0.9265.  $n_D^{20}$  1.4163. Slightly soluble in water (0.082 g/100 g); readily soluble in ethanol, ether. LD<sub>50</sub> orally in rats: 3.0 g/kg. H. F. Smyth, C. P. Carpenter, *J. Ind. Hyg. Toxicol.* 26, 269 (1944).

use: Manuf of esters for artificial flavors, and of hexyl derivatives, especially hexylphenols, hexylresorcinol, etc.

**1735. Caproic Aldehyde. Hexanal; caproaldehyde; hexaldehyde.**  $C_6H_{10}O$ ; mol wt 100.16. C 71.94%, H 12.08%, O 15.97%.  $CH_3(CH_2)_4CHO$ . Prepn: Bagard, *Bull. Soc. Chim.* 1, 307 (1907).

Liquid.  $d_4^{20}$  0.8335.  $bp_{760}$  131°;  $bp_{10}$  28°. Autoxidizes and polymerizes, especially in the presence of traces of acid. LD<sub>50</sub> orally in rats: 4.89 g/kg. Smyth *et al.*, *Arch. Ind. Hyg. Occup. Med.* 10, 61 (1954).

**1736. Caprolactam. Hexahydro-2H-azepin-2-one;  $\epsilon$ -caprolactam; 2-oxohexamethyleneimine; 2-keto-hexamethyleneimine; aminocaproic lactam.**  $C_6H_{11}NO$ ; mol wt 113.16. C 61.68%, H 9.80%, N 12.39%, O 14.14%. Prepn: Wallach, Ann. 312, 187 (1900); 343, 43 (1905); Ruzicka *et al.*, *Helv. Chim. Acta* 4, 477 (1921); Eck, Marvel, *J. Biol. Chem.* 106, 37 (1934); Marvel, Eck, *Org. Syn. coll. vol. II*, 371 (1943); Lazier, Rigby, U.S. pat. 2,234,566 (1941 to du Pont); Black, U.S. pat. 2,249,177 (1941 to I. G. Farben); Ger. pat. 739,953 (1943); 745,224 (1943); P. Smith, *J. Am. Chem. Soc.* 70, 320 (1948); E. Schmitz *et al.*, *J. Prakt. Chem.* 319, 24 (1977). Purification: Kampschmidt, U.S. pat. 3,066,052 (1957 to Stamicarbon N. V.). Stabilization with stabilizers: Indest *et al.*, U.S. pat. 2,884,414 (1959 to Vereinigte Glanzstoff-Fabriken). Reviews: CIOS Repts. no. 22 and File XXXIII/Synthetic Fiber Developments in Germany, parts I & II; K. Kahr *et al.* in *Ullmann's Encyclopädie der Technischen Chemie* vol. 9, E. Bartholome *et al.*, Eds. Verlag Chemie, Weinheim, 4th ed., 1975) pp 96-114.



Hygroscopic leaflets from petr ether, mp 70°.  $d_4^{20}$  (liq) 0.92.  $bp_{50}$  180°;  $bp_3$  100°. Viscosity at 78° = 9 centipoises. Inf. pt. open cup: 257°F (125°C). Freely sol in water, ethanol, ether, tetrahydrofurfuryl alcohol, diethylformamide. Also sol in chlorinated hydrocarbons, cyclohexene, petroleum fractions. A 70% aq soln has  $d_4^{20}$  0.91.  $n_D^{20}$  1.4965;  $n_D^{20}$  1.4935. LD<sub>50</sub> orally in rats: 2.14 g/kg. H. F. Smyth *et al.*, *Am. Ind. Hyg. Assoc. J.* 30, 470 (1969). use: Manuf of synthetic fibers of the polyamide type (Petr. solvent for high mol wt polymers).

**1737. Caproyl Chloride. Hexanoyl chloride.**  $C_6H_{11}ClO$ ; mol wt 134.61. C 53.54%, H 8.24%, Cl 26.34%, O 11.89%.  $(CH_2)_4COCl$ . Prepn: Brown, *J. Am. Chem. Soc.* 60,

1325 (1938). Manuf: Wygant, U.S. pat. 2,806,061 (1957 to Monsanto).

Liquid, bp 151-153°. fp -87.3°.  $d_4^{20}$  0.9805.  $n_D^{20}$  1.4286. Dec by water or alcohol. Sol in ether, chloroform.

**1738. Caprylene. 1-Octene; octylene.**  $C_8H_{16}$ ; mol wt 112.21. C 65.63%, H 14.37%.  $CH_3(CH_2)_6CH=CH_2$ . Prepn from appropriate alkylmagnesium bromide and allyl bromide or chloride: Geisler, Pilz, *Ber.* 95, 96 (1962); from formaldehyde or paraformaldehyde and triphenyl(phenylmethylene)phosphorane: Hauser *et al.*, *J. Org. Chem.* 28, 372 (1963); by catalytic dehydration of 2-octanol: Lundeen, Hoozer, *J. Am. Chem. Soc.* 85, 2180 (1963).

Liquid, bp 121°,  $bp_{100}$  61.5-61.7°. mp -102°.  $d_4^{20}$  0.7149,  $d_4^{25}$  0.7109.  $n_D^{20}$  1.4087,  $n_D^{25}$  1.4062. Flash pt, open cup: 70°F (21°C). Practically insol in water; misc with alcohol, ether.

**1739. Caprylic Acid. Octanoic acid.**  $C_8H_{16}O_2$ ; mol wt 144.21. C 66.63%, H 11.18%, O 22.19%.  $CH_3(CH_2)_6COOH$ . Prepn from 1-heptene: Dupont *et al.*, *Compt. Rend.* 240, 628 (1955); by oxidation of octanol: Langenbeck, Richter, *Ber.* 89, 202 (1956). Manuf: Alexander, U.S. pat. 2,821,534 (1958 to GAF); McAlister *et al.*, U.S. pat. 3,053,869 (1962 to Standard Oil Co., Indiana). Review: *Fatty Acids Part 1*, K. S. Markley, Ed. (Interscience, New York, 2nd ed., 1960) pp 34, 38.

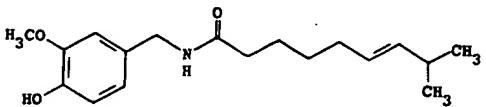
Oily liquid, bp 239.7°. Slightly unpleasant, rancid taste. mp 16.7°.  $d_4^{20}$  0.910.  $n_D^{20}$  1.4280. Very slightly sol in water (0.068 g/100 g at 20°); freely sol in alcohol, chloroform, ether, carbon disulfide, petr ether, glacial acetic acid. LD<sub>50</sub> orally in rats: 10,080 mg/kg. P. M. Jenner *et al.*, *Food Cosmet. Toxicol.* 2, 327 (1964).

use: An intermediate in manuf of esters used in perfumery; in manuf of dyes, etc.

**1740. Caprylic Aldehyde. Octanal; caprylaldehyde; octaldehyde.**  $C_8H_{16}O$ ; mol wt 128.21. C 74.94%, H 12.58%, O 12.48%.  $CH_3(CH_2)_6CHO$ . Prepn: Stephen, *J. Chem. Soc.* 127, 1874 (1905).

Liquid.  $d_4^{20}$  0.821.  $bp_{760}$  163.4°;  $bp_{10}$  72°;  $bp_3$  60°.  $n_D^{20}$  1.41667. Slightly sol in water; misc with alc. ether.

**1741. Capsaicin. N-[4-Hydroxy-3-methoxyphenyl]methylyl-8-methyl-6-nonenamide; trans-8-methyl-N-vanillyl-6-nonenamide; N-(4-hydroxy-3-methoxybenzyl)-8-methyl-6-nonen-6-enamide.**  $C_{16}H_{21}NO_3$ ; mol wt 305.40. C 70.78%, H 8.91%, N 4.59% O 15.72%. Pungent principle in fruit of various species of *Capsicum*, Solanaceae. Isoln from paprika and cayenne: Thresh, *Pharm. J. and Trans.* 7, 21 (1876); Micko, *Z. Nahr. Genusse.* 1, 818 (1898). See Beilstein 13, suppl. I, 322. Early structure study: Nelson, *J. Am. Chem. Soc.* 42, 597 (1920). Synthesis: Späth, Darling, *Ber.* 63, 737 (1930); L. Crombie *et al.*, *J. Chem. Soc.* 1955, 1025; O. P. Vig *et al.*, *Indian J. Chem.* 17B, 558 (1979). Constitution and biosynthesis: D. J. Bennet, E. W. Kirby, *J. Chem. Soc. C* 1968, 442. Pharmacology: Molnar *et al.*, *Acta Physiol.* 35, 369 (1969). Capsaicin is a powerful irritant; administration causes intense pain in humans and exptl animals. Prolonged treatment causes insensitivity to painful stimuli; in newborn rats it induces selective degeneration of certain primary sensory neurones which mediate chemogenic pain, see G. Jancso *et al.*, *Nature* 270, 741 (1977); R. Gamse, *Arch. Pharmacol.* 320, 205 (1982); P. Holzer *et al.*, *Neurosci. Letters* 31, 253 (1982). Capsaicin pretreatment also induces long-lasting desensitization of airway mucosa to various mechanical and chemical irritants: J. M. Lundberg, A. Saria, *Nature* 302, 251 (1983). Reviews: Molnar, *Arzneimittelforsch.* 15, 718 (1965); Walker, Gavern, *Mfg. Chem. Aerosol News* 39 (6), 35 (1968); R. M. Virus, G. F. Gebhart, *Life Sci.* 25, 1273 (1979); Y. Monserenusom *et al.*, *CRC Crit. Rev. Toxicol.* 10, 321-339 (1982).



Monoclinic, rectangular plates, scales from petr ether, mp 65°.  $bp_{0.01}$  210-220° (air-bath temp). uv max: 227, 281 nm

U U U U U U U U  
M M M M M M M M  
J J J J J J J J  
P P P P P P P P